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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/288,326	04/08/99	SACHS	G 17282 VB

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HM12/0327

EXAMINER	
CLEMENS,K	
ART UNIT	**PAPER NUMBER**
1644	14

DATE MAILED: 03/27/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/288,326	Applicant(s) SACHS ET AL.	
	Examiner Karen Clemens	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4/30/00* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☒ Other: *Also PTO-1449 filed 1/23/01* .

DETAILED ACTION

1. The request filed 1/23/01 (Paper No. 14) for a continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent application No. 09/288,326 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 1-24 are pending and under examination.

The Examiner withdraws the species restriction requirement between SEQ ID NOs: 2, 3, 4, 5 and 6 in claims 9-12 since they are subsets of a single larger polypeptide, CCK (Cholecystokinin).

Applicant's species election in Paper No. 6 of a specific *translocation element* comprising the N-terminal half of the heavy chain of a *Clostridium botulinum* neurotoxin and a specific *therapeutic element* cleaving a SNARE protein comprising the light chain of BoNT/A or E, cleaving SNAP-25 and a specific *spacer moiety* comprising a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region such as in SEQ ID NO:11 is reiterated. Nonelected species of therapeutic elements, translocation elements and spacer moieties are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

3. The following are new grounds of rejection.

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-24 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a composition for the treatment of acute pancreatitis comprising a *binding element* able to specifically bind a pancreatic cell surface marker, a *translocation element* able to facilitate transfer of a polypeptide across a vesicular membrane, a *therapeutic element* able, when present in the cytoplasm, to inhibit enzymatic secretion by said pancreatic cell and the said composition additionally with a *spacer moiety* separating the binding element from the translocation element in which the spacer moiety consists of a hydrocarbon, a polypeptide other than an immunoglobulin hinge region, and a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.

However, Applicants disclosure is limited to the *binding elements of SEQ ID NO:2-6* which bind the pancreatic CCK (cholecystokinin) receptor, *translocation elements* that consist of the *N-terminal domain of the heavy chain of a clostridial neurotoxin, therapeutic elements* that consist of the *light chain of a clostridial neurotoxin* and a *spacer moiety that consists of SEQ ID NO:11*. The Applicant has not disclosed, nor does the art recognize, a correlation or relationship between the structure of the binding element, the translocation element, the therapeutic element or the spacer region and their respective functions, essential to the instant invention, and one skilled in the art could not readily envisage the genus of binding elements, translocation elements, therapeutic elements and spacer regions as claimed. Consequently, one of skill in the art would not recognize the Applicants to be in possession of the genus of *binding elements*, *translocation elements*, *therapeutic elements* and *spacer regions* as claimed.

Therefore, the claimed invention is not described in such a way as to reasonably convey to one of ordinary skill in the art that the inventor, at the time the application was filed, had possession of the invention. See *Regents of the University of California v. Eli Lilly & Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).* Applicant is also directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

4. The following is a quotation of 35 U.S.C. §103 which forms the basis for all obviousness rejections set forth in this Office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as

a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

A. Claims 1-12 are rejected under 35 U.S.C. §103(a) as being unpatentable over Shone et al. (WO 98/07864, see IDS, PTO form 1449) in view of Gaisano et al. (*Gastroenterology* 111:1161-1669, and the accompanying editorial on page 1770), Kennedy et al. (*J. Biol.Chem.* 272(5):2920-2926, see IDS, PTO Form 1449) and Ganong (In: *Review of Medical Physiology*, Chapter 26, page 446).

Shone et al. teach a composition comprising a *binding element* which binds to cell surface markers or receptor (see page 7, last paragraph concluding on page 8 and page 4, 3rd paragraph in particular), a *translocation element* able to facilitate the transfer of a polypeptide across a vesicular membrane (see page 1, 3rd paragraph in particular) and a *therapeutic element* which, when present in the cytoplasm, inhibits exocytosis (enzymatic secretion is pancreatic acinar cells) (see page 5, 2nd paragraph in particular). More specifically, Shone et al. teach that this composition comprises a *binding element* that is a ligand for *binding* or targeting the desired cells via the cell surface marker or receptor, a *translocation element* which is the amino terminal region of the heavy chain of a clostridial neurotoxin which is important for *translocation* of the composition across cellular membranes and a *therapeutic element* comprising the light chain of the clostridial neurotoxin. Shone et al. teach that this *therapeutic element* cleaves one or more vesicle or plasma-membrane associated proteins (SNAREs) essential to the specific cellular process of exocytosis, and cleavage of these proteins results in inhibition of exocytosis. Shone et al. further teach that the cell or cells affected are *not* restricted to a particular type or subgroup but can include *both neuronal and non-neuronal cells* and that the activity of the clostridial neurotoxins in inhibiting exocytosis has, indeed, been observed almost universally in eukayotic cells expressing a relevant cell surface receptor which can bind to the composition, in which the binding element for neuronal cells is found in the carboxyl terminus of the heavy chain of clostridial neurotoxins, which is specifically *removed* in this composition to accommodate a binding element for binding to other neuronal or non-neuronal cell types (see page 4, 3rd paragraph and page 7, 2nd paragraph in particular). Shone et al. further teach that the *therapeutic element* preferably exhibits protein cleavage activity specific for a substrate selected from *one or more* of the SNARE proteins SNAP-25, synaptobrevin/VAMP and syntaxin, and that the therapeutic element is preferably derived from botulism or tetanus toxin (both clostridial neurotoxins). It was well known in the art at the time of the invention that different toxin types (e.g. botulinum type A, botulinum type B, tetanus toxin, etc.) of clostridial neurotoxins cleave different subsets of the evolutionarily conserved SNARE proteins.

Shone et al. do not teach the composition for the treatment of acute pancreatitis in a mammal in which the *binding element* specifically binds a pancreatic cell surface marker under physiological conditions and the *therapeutic element*, when present in the cytoplasm of a pancreatic cell, inhibits enzymatic secretion by said pancreatic cell. Shone et al. further do not teach that the said pancreatic cell is an acinar cell and said cell surface marker is a CCK receptor and the binding element comprises the CCK peptides SEQ ID NO:2-6.

However Gaisano et al. teach that exocytosis involving the SNARE protein synaptobrevin/VAMP may play an important role in regulating *enzyme secretion* from pancreatic acinar cells (see abstract in particular). Gaisano et al. teach that molecules that regulate the docking and fusion (exocytosis) of the neuronal synaptic vesicle to the plasma membrane (SNARE proteins) are also used in pancreatic acinar cells in the fusion of the secretory granule (zymogen) with the plasma membrane and that cleavage of these SNARE proteins can inhibit exocytosis and enzyme secretion from the pancreatic acinar cell (see page 1661 in particular). Gaisano et al. teach that in an earlier study they found that the clostridial tetanus neurotoxin light chain cleaved the synaptobrevin/VAMP molecule and inhibited enzyme secretion from pancreatic acinar cells once they were permeabilized by streptolysin O, (see page 1661, column 2, last paragraph in particular) a common method to introduce the neurotoxin light chain (therapeutic element) into the cytoplasm of the cells without requiring a cell surface receptor binding element for binding and internalization (see accompanying editorial, page 1711 last paragraph and concluding on page 1712). It is well known in the art that acute pancreatitis is due to the inflammation of the pancreas and is associated with the "escape" of pancreatic enzymes from acinar cells into surrounding tissues.

Kennedy et al. teach that CCK binds to CCK-A receptors on pancreatic acinar cells with high affinity (see page 2920, column 2, 2nd paragraph in particular) and Ganong teach that the major physiological forms of CCK include CCK-58 (SEQ ID NO:2), CCK-39 (SEQ ID NO:3), CCK-33 (SEQ ID NO:4), CCK-12 (SEQ ID NO:5) and CCK-8 (SEQ ID NO:6) (see page 446, column 1, 3rd paragraph in particular).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to design a composition consisting of a *binding element*, which specifically binds a cell surface receptor, a *translocation element*, which is able to facilitate the transfer of a polypeptide across a vesicular membrane, and a *therapeutic element* which, when present in the cytoplasm, inhibits exocytosis by

cleaving one or more of the evolutionarily conserved SNARE proteins, syntaxin, SNAP-25 and VAMP as taught by Shone et al. for inhibiting exocytosis and therefore enzyme secretion, which similarly requires one of the SNARE proteins, in pancreatic acinar cells as taught by Gaisano et al. in which the binding element consists of SEQ ID NOs: 2, 3, 4, 5 and 6 which bind the CCK-A receptors on pancreatic acinar cells with high affinity as taught by Ganong and Kennedy et al.

One of skill in the art would have been motivated to use a composition comprising a binding element, a translocation element and a therapeutic element which specifically blocks exocytosis as taught by Shone et al. and which specifically targets the CCK-A receptor on pancreatic acinar cells by using CCK peptides as the binding element as taught by Kennedy et al. and Ganong, and once internalized inhibits exocytosis and enzymatic secretion from the pancreatic cell in which the therapeutic element cleaves the SNARE protein VAMP, which is involved in the evolutionarily conserved process of vesicle docking found also in neuronal cells as taught by Gaisano et al. One of skill in the art would have been motivated to use this composition which would block enzyme secretion of the pancreatic acinar cells to treat acute pancreatitis which is well known in the art to be associated with the "escape" of pancreatic enzymes from acinar cells into surrounding tissues.

B. Claims 13-24 are rejected under 35 U.S.C. §103(a) as being unpatentable over Shone et al. (WO 98/07864), Gaisano et al. (*Gastroenterology* 111:1161-1669, and the accompanying editorial on page 1770), Kennedy et al. (*J. Biol.Chem.* 272(5):2920-2926) and Ganong as applied to claims 1-12 and further in view of Foster et al. (WO96/33273, see IDS, PTO Form 1449) and Dangl et al. (of record, *EMBO J.* 7(7):1989-94, 1988).

Shone et al., Gaisano et al., Kennedy et al. and Ganong have been discussed supra.

However Shone et al., Gaisano et al., Kennedy et al. and Ganong do not teach a composition further comprising a *spacer moiety* which separates the binding element from the translocation element. The combined references further do not teach that the spacer moiety comprises a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region of SEQ ID NO:11.

However, Foster et al. teach a composition comprising a binding element to a neuronal cell surface marker (see page 9, lines 19-21 and page 12, line 25 to page 13, line 6, in particular), a translocation

element consisting of the N-terminal half of the heavy chain of a clostridial neurotoxin (C. botulinum or C. tetani; see page 9, lines 8-12 and page 12, lines 1-24 in particular) a therapeutic element consisting of the light chain of a clostridial neurotoxin (C. botulinum or C. tetani) capable of cleaving the SNARE protein, synaptobrevin, syntaxin or SNAP-25 (see page 12, lines 13-19 in particular) which will inhibit vesicle exocytosis and secretion, and a *spacer moiety* separating the binding element and the translocation element and which are used to link the two elements (see page 13, lines 18-24 in particular).

Foster et al. do not teach a spacer moiety specifically comprising a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region (such as SEQ ID. NO:11).

However, Dangl et al., teach that the immunoglobulin hinge region (SEQ ID NO:11) allows for flexible movement of the antigen binding regions of the immunoglobulin molecule such that two antigen binding sites can move relative to each other to bind determinants separated by different distances and orientations (see page 1991, Table 1 in particular). Dangl et al. further teach that this hinge region may function as a spacer, facilitating a proper spatial relationship between the Fab and Fc regions, allowing for both antigen binding and Fc effector functions such as complement activation (see page 1989, introduction, and page 1991, Table 1 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to design a composition with a spacer moiety separating the binding element and translocation elements which link the two elements as taught by Foster et al. in which the spacer moiety comprises an immunoglobulin hinge region as taught by Dangl et al. One having ordinary skill in the art at the time the invention was made would have been motivated to use a spacer region for connecting the binding element with the translocation element in which the spacer region is an immunoglobulin hinge region (SEQ ID NO:11) since the hinge region allows for a high degree of flexibility in the movement of the domains, such as the translocation and binding elements, which it interconnects.

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Clemens whose telephone number is (703) 308-8365. The examiner can normally be reached Monday through Friday from 8:00 am to 5:00 pm. A message may be left on the examiner's voice

mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Karen Clemens, Ph.D.
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Technology Center 1600
March 21, 2001

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